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Chronic Hepatitis A With Persistent Viral Replication

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Hepatitis A virus (HAV) usually causes an acute self-limited illness. This report describes a patient with hepatitis A whose serum aminotransferase activities remained above normal and whose serum was persistently positive for immunoglobulin (Ig) M class anti-hepatitis A 31 months after the onset of hepatitis. Liver biopsy carried out 11 months after the onset of hepatitis showed histological changes consistent with chronic hepatitis of moderate severity. HAV RNA was detected by polymerase chain reaction (PCR) in feces collected at the time of the liver biopsy. Furthermore, the patient developed esophageal varices 25 months after the onset of hepatitis. We believe this to be the first reported case in which persistent replication of HAV is implicated in chronic hepatitis with the potential to develop into liver cirrhosis.

KEY WORDS: HAV RNA, chronic hepatitis, IgM-HA antibody

INTRODUCTION

It is generally believed that hepatitis A virus (HAV) causes acute self-limiting hepatitis that never leads to chronic hepatitis or a chronic carrier state. However, McDonald et al. [1989] reported the case of a young male with acute hepatitis A who was serologically positive for IgM anti-HAV for more than 1,000 days. Liver biopsy undertaken 2 years after the onset of hepatitis showed that he had chronic active hepatitis with progressive fibrosis. In that report, however, persistent HAV replication was not demonstrated in the patient and that chronic hepatitis caused by HAV is not certain.

In the present report we describe a case histologically confirmed to be chronic hepatitis with moderate severity and the potential to develop liver cirrhosis. Virological evidence is presented of persistent HAV replication for more than 6 months after the diagnosis of hepatitis, and no evidence of infection with other hepatitis viruses.

Method

Commercial kits (Abbott Laboratories, North Chicago, IL) were used to test for immunoglobulin(Ig) M antibody to HAV (anti-HA), hepatitis B surface antigen (HBsAg), antibody to HBsAg(anti-HBs), antibody to HB core antigen (anti-HBc), HBeAg, antibody to HBeAg (anti-HBe), and antibody to hepatitis D virus (anti-HD). The presence of antibody to hepatitis C virus (anti-HCV) was determined by a second-generation commercial kit (Ortho Diagnostics, Tokyo, Japan). The presence of antibody to human immunodeficiency virus (anti-HIV) was tested by a commercial kit (Fujirebio, Tokyo, Japan). HCV RNA was tested by nested polymerase chain reaction (PCR), using two sets of primers deduced from the 5′-noncoding region of HCV [Okamoto et al., 1990]. Hepatitis B virus (HBV) DNA was tested by PCR using a set of primers deduced from the HBsAg region of HBV DNA.

HAV RNA was detected by the reverse transcription (RT)-PCR method previously reported [Yotsuyanagi et al., 1993]. Briefly, HAV RNA was amplified with two different sets of primers. One set of primers described by Cohen et al. [1987] was deduced from the 5′-noncoding region of the HAV genome. The other set of primers described by Jansen et al. [1990] was deduced from the VP3 region. PCR products were analyzed by electrophoresis in 6% polyacrylamide gels and by ethidium bromide staining.

Case

A 48-year-old male patient was admitted to Showa University Fujigaoka Hospital with marked jaundice and general malaise. There was no family history of liver disease, prior history of jaundice, nor known blood transfusion or intravenous drug abuse. The patient reported having eaten raw fish several times a month before admission. He complained of becoming fatigued easily, and had had high fever 7 days before admission. He consulted a family physician and was found to be jaundiced. On March 15, 1993 he was referred to our hospital and admitted.

Physical examination revealed marked jaundice and a mildly enlarged liver. On neurological examination the patient was alert and fully oriented. Hematological tests

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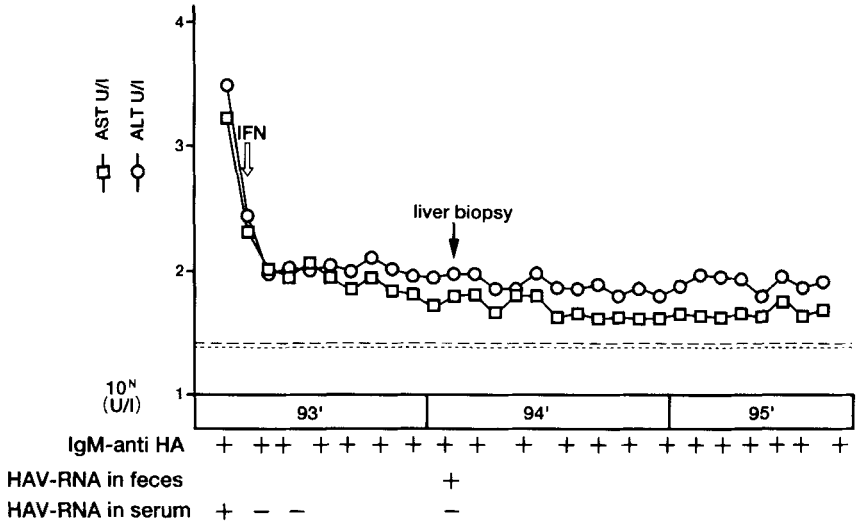

Fig. 1. Clinical course of a 48-year-old male patient with type A hepatitis. Fluctuation of AST and ALT activity is shown along with the change in IgM-HA and HAV RNA positivity. Upper limit of normal for AST and ALT indicates a dotted line and an interrupted line, respectively.

revealed a red blood cell (RBC) count at 573 × 10^4/mm^3 white blood cells (WBC) at 8,700/mm^3, platelets at 19.1 × 10^4/mm^3, prothrombin time (PT) at 38.0%, activated partial thromboplastin time at 61.2%, fibrinogen at 282 mg/dl, fibrin/fibrinogen degradation products at 582 ng/ml (normal < 100 ng/ml), antithrombin III at 31%, and hepaplastin test at 24.9%. Blood chemistry tests showed that total protein was 7.1 g/dl, albumin 3.5 g/dl, blood urea nitrogen (BUN) 10.6 mg/dl, total bilirubin 12.8 mg/dl, aspartate aminotransferase (AST) 1,705 U/l, alanine aminotransferase (ALT) 3,230 U/l, lactate dehydrogenase 784 U/l, alkaline phosphatase 269 U/l, γ-glutamyl transpeptidase 273 U/l, choline esterase 171 U/l (normal 135–413 U/l), and total cholesterol 93 mg/dl. Virological study found the patient positive for IgM anti-HA, and negative for HBsAg, HBeAg, anti-HBe, anti-HBc (1:200 dilution), HBV DNA polymerase (DNA-P) 0 cpm/ml, and both anti-HCV and HCV RNA. AST and ALT decreased to 198 U/l and 207 U/l, respectively, at 10 days after admission. PT had not improved and total bilirubin had risen to 18.3 mg/dl.

Based upon the experimental observation that interferon (IFN) is effective in the treatment of HAV [Vallbracht and Flehming, 1985], IFN-β (Feron, Toray Medical Co., Tokyo, Japan) at a daily dose of 3 MU was started 10 days after admission. The patient's liver function improved after the start of IFN treatment, and IFN was discontinued after 2 weeks. The total IFN administered was 42 MU. PT rose to 61% and serum total bilirubin decreased to 5.6 mg/dl. The patient recovered and was discharged on May 20, 1993.

ASTL and ALT levels, however, fluctuated between 41 and 138 U/l and IgM anti-HA was persistently positive after discharge (Fig. 1). The patient underwent liver biopsy on February 24, 1994, showing findings typical of chronic hepatitis of moderate severity (Fig. 2) [Ludwig, 1993]. We performed PCR to detect HAV RNA using two different sets of primers. HAV RNA was detected with both sets of primers in the patient's serum at the onset of hepatitis as well as in his feces 11 months after the onset of hepatitis (Fig. 3). Serum HAV RNA was negative at the latter time. Endoscopy in April 1995 (14 months after onset) revealed esophageal varices.

HBV DNA, HCV RNA, anti-HD, anti-HIV, antinuclear antibodies (ANA), and liver-kidney microsome antibodies (anti-LKM) were not detected and the serum level of IgG was 1,830 mg/dl at admission. Serological markers of HBV and anti-HCV were repeatedly negative. Serum aminotransferase activities fluctuated at above normal limits and IgM anti-HAV continued to be positive for more than 31 months after the onset of hepatitis. In October 1995, AST and ALT were 50 and 75 U/l, respectively.

DISCUSSION

We report a rare patient in whom histologically confirmed chronic hepatitis of moderate severity is associated with replication of HAV persisting for more than 6 months. The patient was neither immunologically compromised nor had he received immunosuppressive agents. Coinfection by other known hepatitis viruses was excluded by specific virological tests. Autoimmune hepatitis was excluded by the negative results for ANA and anti-LKM, and by his normal IgG level.

The mechanism of chronicity of type A hepatitis in this patient is not known. We have, however, seen increasing numbers of patients with fulminant hepatitis A who, in contrast to the classic clinical features, show prolonged hepatocyte destruction and liver failure with persistent elevated IgM levels that sometimes require IFN treatment [Yoshiba et al., 1994]. This patient also received IFN therapy for 2 weeks that seemed to be effective in

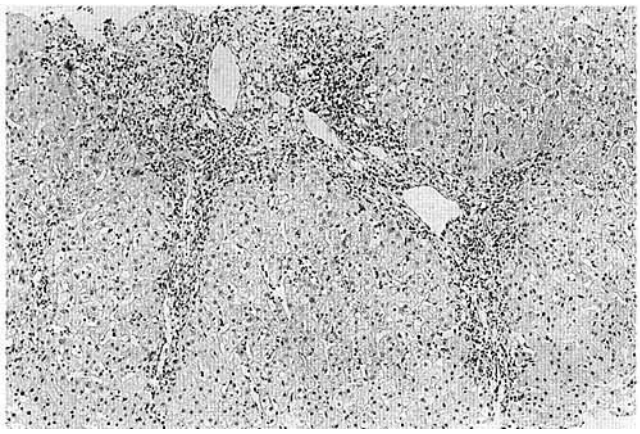

Fig. 2. Liver biopsy specimen obtained on February 24, 1994. Portal expansion and moderate interface hepatitis as well as slight lobular activity, consistent with chronic hepatitis of moderate severity. HE ×200.

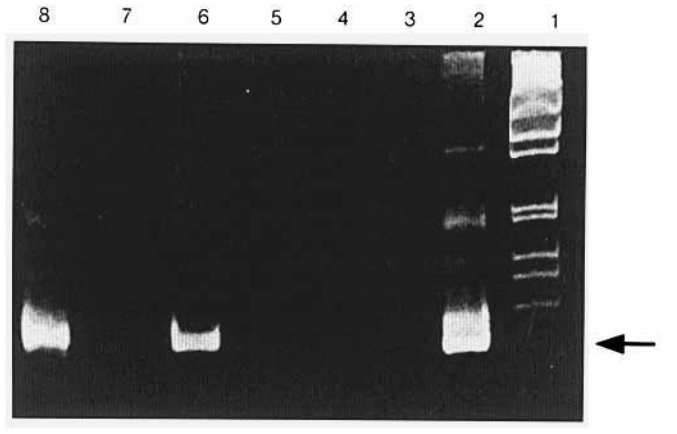

Fig. 3. Detection of HAV RNA by RT-PCR. **Lane 1:** Molecular weight markers. **Lanes 2–5:** RNA from patient's serum. **Lane 6:** Positive control obtained from HAV cultures. **Lane 7:** Negative control. **Lane 8:** RNA from a patient's feces. PCR products of HAV RNA have 272 base pairs in size.

improving severe liver dysfunction. The treatment was of a limited value, however, in eradicating HAV.

We have treated six cases with fulminant hepatitis A who showed a prolonged elevation of IgM anti-HA and aminotransferase activities with IFN. The total amount of administered IFN in these six cases was 138 MU (105-267 MU) which was greater than that in the present case. IFN seemed effective in improving liver function and eradicating HAV in these patients because all survived, resulting in the final elimination of HAV. Although IFN seemed effective in improving liver function, the total amount may have been too small for the eradication of HAV in the present case.

Chronicity of hepatitis was established by liver biopsy performed 11 months after the onset of hepatitis. Aminotransferase activities fluctuated persistently with elevated IgM anti-HA level as late as 31 months after the onset of hepatitis. Furthermore, esophageal varices were observed 25 months after the onset of hepatitis. The presence of liver cirrhosis is not ascertained at present. Above observations imply, however, that hepatitis in this patient is not merely prolonged but has the potential to develop into liver cirrhosis.

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